In the Specification:

Please amend the specification as shown:

Please delete the paragraph, page 15, lines 22-27, through page 16, lines 1-8, and replace it with the following paragraph:

Ser

Gly-Ser

Gly-Gly-Ser

Ser-Gly-Gly

Gly-Gly-Gly-Ser **(SEQ ID NO: 129)**

Ser-Gly-Gly-Gly **(SEQ ID NO: 130)**

Gly-Gly-Gly-Gly-Ser **(SEQ ID NO: 131)**

Ser-Gly-Gly-Gly-Gly **(SEQ ID NO: 132)**

Gly-Gly-Gly-Gly-Gly-Ser **(SEQ ID NO: 133)**

Ser-Gly-Gly-Gly-Gly-Gly **(SEQ ID NO: 134)**

Gly-Gly-Gly-Gly-Gly-Gly-Ser **(SEQ ID NO: 135)**

Ser-Gly-Gly-Gly-Gly-Gly-Gly **(SEQ ID NO: 136)**

$(Gly\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Ser)_n$ and **(SEQ ID NO: 137)**

$(Ser\text{-}Gly\text{-}Gly\text{-}Gly\text{-}Gly)_n$ **(SEQ ID NO: 138)**

Please delete the paragraph on page 32, lines 14-25, and replace it with the following paragraph:

The nucleotide sequence of the gene encoding the L chain V region from the mouse antibody MABL-1 **(SEQ ID NO: 85)**, which is included in the plasmid pGEM-M1L, is shown in SEQ ID No. 5.

The nucleotide sequence of the gene encoding the H chain V region from the mouse antibody MABL-1 **(SEQ ID NO: 86)**, which is included in the plasmid pGEM-M1H, is shown in SEQ ID No. 6.

The nucleotide sequence of the gene encoding the L chain V region from the mouse antibody MABL-2 **(SEQ ID NO: 87)**, which is included in the plasmid pGEM-M2L, is shown in SEQ ID No. 7.

The nucleotide sequence of the gene encoding the H chain V region from the mouse antibody MABL-2 **(SEQ ID NO: 88)**, which is included in the plasmid pGEM-M2H, is shown in SEQ ID No. 8.

Please delete the paragraph on page 40, lines 8-20, and replace it with the following paragraph:

A DNA fragment of 843 bp produced by the second PCR was purified and digested by NcoI and EcoRI. The resultant DNA fragment was cloned into pSCFVT7 vector. The expression vector pSCFVT7 contains a pelB signal sequence suitable for E. coli periplasmic expression system (Lei, S. P., et al., J. Bacteriology, 169, 4379-4383, 1987). After the DNA sequencing, the plasmid containing the DNA fragment encoding correct amino acid sequence **(SEQ ID NO: 90)** of the reconstructed single chain Fv of antibody MABL-1 is designated as "pscM1" (see Figure 5). The nucleotide sequence and the amino acid sequence of the reconstructed single chain Fv of antibody MABL-1 contained in the plasmid pscM1 are shown in SEQ ID No. 20.

Please delete the paragraph on page 41, lines 19-27, through page 42, lines 1-9, and replace it with the following paragraph:

The PCR product was purified using the QIAquick PCR Purification Kit (QIAGEN) and digested by SalI and MboII to obtain a DNA fragment encoding the N-terminal of the reconstructed single chain Fv of antibody MABL-1 The pscM1 vector was digested by MboII and EcoRI to obtain a DNA fragment encoding the C-terminal of the reconstructed single chain Fv of antibody MABL-1. The SalI-MboII DNA fragment and the MboII- EcoRI DNA fragment were cloned into pCHO1-Igs vector. After DNA sequencing, the plasmid comprising the desired DNA sequence was designated as "pCHOM1" (see Figure 6). The expression vector, pCHO1-Igs, contains a mouse IgG1 signal sequence suitable for the secretion-expression system in mammalian cells

(Nature, 322, 323-327, 1988). The nucleotide sequence and the amino acid sequence **(SEQ ID NO: 91)** of the reconstructed single chain Fv of antibody MABL-1 contained in the plasmid pCHOM1 are shown in SEQ ID No. 23.

Please delete the paragraph on page 42, lines 10-21, and replace it with the following paragraph:

The reconstructed single chain Fv of antibody MABL-2 was prepared in accordance with the aforementioned Example 5.1. Employed in the first PCR step were plasmid pGEM-M2H encoding the H chain V region of MABL-2 (see Example 2) instead of pGEM-M1H and plasmid pGEM-M2L encoding the L chain V region of MABL-2 (see Example 2) instead of pGEM-M1L, to obtain a plasmid pscM2 which comprises a DNA fragment encoding the desired amino acid sequence **(SEQ ID NO: 92)** of the single chain Fv of antibody MABL-2. The nucleotide sequence and the amino acid sequence of the reconstructed single chain Fv of antibody MABL-2 contained in the plasmid pscM2 are shown in SEQ ID No. 24.

Please delete the paragraph on page 42, lines 22-27, through page 43, lines 1-2, and replace it with the following paragraph:

The pscM2 vector was modified by the PCR method to prepare a vector, pCHOM2, for the expression in mammalian cells which contains the DNA fragment encoding the correct amino acid sequence of reconstructed the single chain Fv of antibody MABL-2. The nucleotide sequence and the amino acid sequence **(SEQ ID NO: 93)** of the reconstructed single chain Fv of antibody MABL-2 contained in the plasmid pCHOM2 are shown in SEQ ID No. 25.

Please delete the paragraph on page 45, lines 13-27, through page 46, lines 1-3, and replace it with the following paragraph:

The anti-FLAG antibody adjusted to 1 μg/ml was added to each well on 96-well plate and incubated at 37°C for 2 hours. After washing, blocking was performed with 1% BSA-PBS. After incubating and washing at a room temperature, the culture supernatant of COS7 cells into which the secretion-type human IAP antigen gene (SEQ ID No. 26; **amino acid sequence disclosed as SEQ ID NO: 94**) had been introduced was diluted with PBS into twofold volume and added to each well. After incubating and washing at a room temperature, a mixture of 50 μl of the biotinized MABL-2 antibody adjusted to 100 ng/ml and 50 μl of sequentially diluted supernatant of the COS7 cells expressing the reconstructed single chain Fv of antibody MABL-2 were added into each well. After incubating and washing at a room temperature, the alkaline phosphatase-conjugated streptoavidin (Zymed) was added into each well. After incubating and washing at a room temperature, the substrate solution (SIGMA) was added and absorbance of the reaction mixture in each well was measured at 405 nm.

Please delete the paragraph on page 51, lines 14-24, and replace it with the following paragraph:

The PCR product was purified using the QIAquick PCR Purification Kit (QIAGEN) and digested by NdeI and EcoRI, and then the resulting DNA fragment was cloned into pSCFVT7 vector, from which pelB signal sequence had been eliminated by the digestion with NdeI and EcoRI. After DNA sequencing, the resulting plasmid comprising a DNA fragment with the desired DNA sequence is designated as "pscM2Dem02" (see Figure 23). The nucleotide sequence and the amino acid sequence **(SEQ ID NO: 95)** of the single chain Fv derived from the antibody MABL-2 contained in the plasmid pscM2Dem02 are shown in SEQ ID No. 29.

Please delete the paragraph on page 61, lines 14-25, and replace it with the following paragraph:

The PCR product was purified using the QIAquick PCR Purification Kit (QIAGEN) and digested by SalI. The resultant DNA fragment was cloned into pBluescript KS^+ vector (Toyobo, Inc.). After DNA sequencing, a plasmid comprising the desired DNA sequence was digested by SalI and the obtained DNA fragment was connected using Rapid DNA Ligation Kit (BOEHRINGER MANNHEIM) to pCHOM2 digested by SalI. After DNA sequencing, a plasmid comprising the desired DNA sequence is designated as "pCHOM2 $(Fv)_2$" (see Figure 34). The nucleotide sequence and the amino acid sequence **(SEQ ID NO: 96)** of the antibody MABL-2 sc $(Fv)_2$ region contained in the plasmid pCHOM2 $(Fv)_2$ are shown in SEQ ID No. 32.

Please delete the paragraph on page 62, lines 7-26, and replace it with the following paragraph:

To construct HL type scFv the PCR procedure was carried out using pCHOM2 $(Fv)_2$ as a template. In the PCR step, a pair of CFHL-F1 primer (SE[~~W~~]**Q** ID NO: 33) and CFHL-R2 primer (SEQ ID NO: 34) or a pair of CFHL-F2 primer (SEQ ID NO: 35) and CFHL-R1 primer (SEQ ID NO: 36) and KOD polymerase were employed. The PCR procedure was carried out by repeating 30 times the temperature cycle consisting of 94°C for 30 seconds, 60°C for 30 seconds and 72°C for 1 minute in order to produce a cDNA for the H chain containing a leader sequence at 5'-end or a cDNA for the L chain containing FLAG sequence at 3'-end thereof. The resultant cDNAs for the H chain and the L chain were mixed and PCR was carried out by repeating 5 times the temperature cycle consisting of 94°C for 30 seconds, 60°C for 30 seconds and 72°C for 1 minute in order using the mixtures as templates and the KOD polymerase. To the reaction mixture were added CFHL-F1 and CFHL-R1 primers and then the PCR reaction was performed by repeating 30 times of the aforementioned temperature cycle to produce a cDNA for HL-0 type without a linker.

Please delete the paragraph on page 65, lines 18-24, and replace it with the following paragraph:

As a typical example of these plasmids, the construction of the plasmid CF2HL-0/pCOS1 is illustrated in Figure 35 and the nucleotide sequence and the amino acid sequence **(SEQ ID NO: 97)** of MABL2-scFv <HL-0> contained in the plasmid are shown in SEQ ID No. 48. Nucleotide sequences and amino acid sequences of the linker regions in these plasmids are also shown in Figure 36 **(bases 400-417 of SEQ ID NO: 48, residues 134-139 of SEQ ID NO: 97 and SEQ ID NOS 109-118, respectively, in order of appearance)**.

Please delete the paragraph on page 67, lines 4-10, and replace it with the following paragraph:

As a typical example of these plasmids, the construction of the plasmid CF2LH-0/pCOS1 is illustrated in Figure 37 and the nucleotide sequence and the amino acid sequence of **(SEQ ID NO: 98)** of MABL2scFv <LH-0> contained in the plasmid are shown in SEQ ID No. 54. Nucleotide sequences and amino acid sequences of the linker regions in these plasmids are also shown in Figure 38 **(bases 385-402 of SEQ ID NO: 54, residues 129-134 of SEQ ID NO: 98 and SEQ ID NOS 119-128, respectively, in order of appearance)**.

Please delete the paragraph on page 80, lines 10-27, through page 81, lines 1-4, and replace it with the following paragraph:

The gene encoding H chain V region of human antibody 12B5 (SEQ ID NO: 99) binding to human MPL was designed by connecting the nucleotide sequence of the gene thereof (SEQ ID NO: 55) at the 5'-end to the leader sequence (SEQ ID NO: 56**; amino acid sequence disclosed as SEQ ID NO: 100**) originated from human antibody gene (Eur. J. Immunol. 1996; 26: 63-69). The designed nucleotide

sequence was divided into four oligonucleotides having overlapping sequences of 15 bp each (12B5VH-1, 12B5VH-2, 12B5VH-3, 12B5VH-4). 12B5VH-1 (SEQ ID NO: 57) and 12B5VH-3 (SEQ ID NO: 59) were synthesized in the sense direction, and 12B5VH-2 (SEQ ID NO: 58) and 12B5VH-4 (SEQ ID NO: 60) in the antisense direction, respectively. After assembling each synthesized oligonucleotide by respective complementarity, the outside primers (12B5VH-S and 12B5VH-A) were added to amplify the full length of the gene. 12B5VH-S (SEQ ID NO: 61) was designed to hybridize to 5'-end of the leader sequence by the forward primer and to have Hind III restriction enzyme recognition site and Kozak sequence, and 12B5VH-A (SEQ ID NO: 62) was designed to hybridize to the nucleotide sequence encoding C-terminal of H chain V region by the reverse primer and to have a splice donor sequence and BamHI restrtiction enzyme recognition site, respectively.

Please delete the paragraph on page 81, lines 23-27, through page 82, lines 1-15, and replace it with the following paragraph:

The HEF-12B5H-gγ1 was digested by restriction enzymes EcoRI and BamHI to produce the gene encoding 12B5VH which was then cloned into an expression vector pCOS-Fd for human Fab H chain to produce pFd-12B5H. The expression vector for human Fab H chain was constructed by amplifying the DNA (SEQ ID NO: 63**; amino acid sequence disclosed in SEQ ID NO: 101**) containing the intron region existing between the genes encoding human antibody H chain V region and the constant region, and the gene encoding a part of the constant region of human H chain by PCR, and inserting the PCR product into animal cell expression vector pCOS1. The human H chain constant region was amplified for the gene under the same conditions mentioned above using as the template HEF- gγ1, as the forward primer G1CH1-S (SEQ ID NO: 64) which was designed to hybridize to 5'-end sequence of intron 1 and to have restriction enzyme recognition sites EcoRI and BamHI and as the reverse primer G1CH1-A (SEQ ID NO: 65) which was designed to hybridize to 3'-end DNA of

human H chain constant region CH1 domain and to have a sequence encoding a part of hinge region, two stop codons and restriction enzyme recognition site Bgl II.

Please delete the paragraph on page 82, lines 16-19, and replace it with the following paragraph:

The nucleotide sequence and amino acid sequence **(SEQ ID NO: 102)** of the reconstructed 12B5H chain variable region which were included in plasmids HEF-12B5H- gγ1 and pFd-12B5H are shown in SEQ ID NO: 66.

Please delete the paragraph on page 82, lines 20-27, through page 83, lines 1-15, and replace it with the following paragraph:

7.2 Construction of the gene encoding 12B5 L chain V region

The gene encoding L chain V region of human antibody 12B5 **(SEQ ID NO: 103)** binding to human MPL was designed by connecting the nucleotide sequence of gene (SEQ ID NO: 67) at the 5'-end to the leader sequence (SEQ ID NO: 68**; amino acid sequence disclosed in SEQ ID NO: 104**) originated from human antibody gene 3D6 (Nuc. Acid Res. 1990: 18; 4927). In the same way as mentioned above the designed nucleotide sequence was divided into four oligonucleotides having overlapping sequences of 15 bp each (12B5VL-1, 12B5VL-2, 12B5VL-3, 12B5VL-4) and synthesized respectively. 12B5VL-1 (SEQ ID NO: 69) and 12B5VL-3 (SEQ ID NO: 71) had sense sequences, and 12B5VL-2 (SEQ ID NO: 70) and 12B5VL-4 (SEQ ID NO: 72) had antisense sequences, respectively. Each of the synthesized oligonucleotides was assembled by respective complementarity and mixed with the external primer (12B5VL-S and 2B5VL-A) to amplify the full length of the gene. 12B5VL-S **(SEQ ID NO: 73)** was designed to hybridize to 5'-end of the leader sequence by the forward primer and to have Hind III restriction enzyme recognition site and Kozak sequence. 12B5VL-A **(SEQ ID NO: 74)** was designed to hybridize to the nucleotide sequence encoding C-terminal of L chain V region by the reverse

primer and to have a splice donor sequence and BamHI restriction enzyme recognition site.

Please delete the paragraph on page 83, lines 16-25, and replace it with the following paragraph:

Performing the PCR as mentioned above, the PCR product was purified by 1.5 % low-melting-temperature agarose gel (Sigma), digested by restriction enzymes BamHI and Hind III, and cloned into an expression vector HEF-gκ for human L chain. After determining the DNA sequence the plasmid containing the correct DNA sequence was named HEF-12B5L-gκ. **The nucleotide sequence and amino acid sequence (SEQ ID NO: 105) of the reconstructed 12B5 L chain V region which were included in plasmid HEF-12B5L-gκ are shown in SEQ ID NO: 75.**

Please delete the paragraph on page 83, lines 26-27, through page 84, lines 1-5, and replace it with the following paragraph:

The reconstructed 12B5 antibody single chain Fv was designed to be in the order of 12B5VH-linker-12B5VL and to have a FLAG sequence **(SEQ ID NO: 76)** at C-terminal to facilitate the detection and purification. The reconstructed 12B5 single chain Fv (sc12B5) was constructed using a linker sequence consisting of 15 amino acids represented by $(Gly_4Ser)_3$ **(SEQ ID NO: 89)**.

Please delete the paragraph on page 84, lines 17-22, and replace it with the following paragraph:

The forward primer 12B5-S (Primer A, **SEQ ID NO: 77**) for H chain V region was designed to hybridize to 5'-end of H chain leader sequence and to have EcoRI restriction enzyme recognition site. The reverse primer HuVHJ3 (Primer B, **SEQ ID NO: 78**) for H chain V region was designed to hybridize to DNA encoding C-terminal of H chain V region.

Please delete the paragraph on page 84, lines 23-27, through page 84, lines 1-2, and replace it with the following paragraph:

The forward primer RHuJH3 (Primer C, **SEQ ID NO: 79**) for the linker was designed to hybridize to DNA encoding the N-terminal of the linker and to overlap DNA encoding the C-terminal of H chain V region. The reverse primer RHuVK1 (Primer D, **SEQ ID NO: 80**) for the linker was designed to hybridize to DNA encoding the C-terminal of the linker and overlap DNA encoding the N-terminal of L chain V region.

Please delete the paragraph on page 85, lines 3-11, and replace it with the following paragraph:

The forward primer HuVK1.2 (Primer E, **SEQ ID NO: 81**) for L chain V region was designed to hybridize to DNA encoding the N-terminal of L chain V region. The reverse primer 12B5F-A for L chain V region (Primer F, **SEQ ID NO: 82**) was designed to hybridize to DNA encoding C-terminal of L chain V region and to have the sequence encoding FLAG peptide (Hopp, T. P. et al., Bio/Technology, 6, 1204-1210, 1988), two transcription stop codons and NotI restriction enzyme recognition site.

Please delete the paragraph on page 85, lines 12-27, and replace it with the following paragraph:

In the first PCR step, three reactions A-B, C-D, and E-F were performed, and the three PCR products obtained from the first step PCR were assembled by respective complementarity. After adding primers A and F the full length DNA encoding the reconstructed 12B5 single chain Fv having the linker consisting of 15 amino acids was amplified (the second PCR). In the first step PCR, the plasmid HEF-12B5H- gγ1 (see Example 7. 1) encoding the reconstructed 12B5H chain V region, pSCFVT7-hM21 (humanized ONS-M21 antibody) (Ohtomo et al., Anticancer Res. 18 (1998), 4311-4316) containing DNA **(SEQ ID NO: 83)** encoding the linker region consisting of Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser **(SEQ ID NO: 107)** (Huston et al.,

Proc. Natl. Acad. Sci. USA, 85, 5879-5883, 1988) and the plasmid HEF-12B5L-gκ (see Example 7. 2) encoding the reconstructed 12B5 L chain V region were used as templates, respectively.

Please delete the paragraph on page 86, lines 23-27, through page 87, lines 1-9, and replace it with the following paragraph:

The DNA fragments produced by the second PCR were purified using 1.5 % low-melting-temperature agarose gel, digested by EcoRI and NotI, and cloned into pCHO1 vector and pCOS1 vector (Japanese Patent Application No. 8-255196). The expression vector pCHO1 was a vector constructed by deleting the antibody gene from DHFR-ΔE-rvH-PM1-f (see WO92/19759) by EcoRI and SmaI digestion, and connecting to EcoRI-NotI-BamHI Adaptor (TAKARA SHUZO). After determining the DNA sequence the plasmids containing the DNA fragment encoding the correct amino acid sequence of reconstructed 12B5 single chain Fv were named pCHO-sc12B5 and pCOS-sc12B5. **The nucleotide sequence and amino acid sequence (SEQ ID NO: 108) of the reconstructed 12B5 single chain Fv included in the plasmids pCHO-sc12B5 and pCOS-sc12B5 are shown in SEQ ID NO: 84.**

Please delete the paragraph on page 92, lines 25-27, and replace it with the following paragraph:

Figure 5 illustrates a structure of an expression plasmid which can be used to express a DNA encoding the single chain Fv of the invention in E. coli. **$(Gly_4Ser)_3$ linker is disclosed as SEQ ID NO: 89**.

Please delete the paragraph on page 93, lines 1-3, through page 84, lines 1-5, and replace it with the following paragraph:

Figure 6 illustrates a structure of an expression plasmid which is used to express a DNA encoding the single chain Fv of the invention in mammalian cells. **$(Gly_4Ser)_3$ linker is disclosed as SEQ ID NO: 89**.

Please delete the paragraph on page 96, lines 4-6, and replace it with the following paragraph:

Figure 23 illustrates a structure of an expression plasmid which can be used to express a DNA encoding the single chain Fv of the invention in E. coli. **$(Gly_4Ser)_3$ linker is disclosed as SEQ ID NO: 89**.

Please delete the paragraph on page 98, lines 13-14, and replace it with the following paragraph:

Figure 36 illustrates a structure of the HL-type polypeptide and amino acid sequences of peptide linkers **(bases 400-417 of SEQ ID NO: 48, residues 134-139 of SEQ ID NO: 97 and SEQ ID NOS 109-118, respectively, in order of appearance)**.

Please delete the paragraph on page 98, lines 19-20, and replace it with the following paragraph:

Figure 38 illustrates a structure of the LH-type polypeptide and amino acid sequences of peptide linkers **(bases 385-402 of SEQ ID NO: 54, residues 129-134 of SEQ ID NO: 98 and SEQ ID NOS 119-128, respectively, in order of appearance)**.

Please delete the paragraph on page 100, lines 5-8, and replace it with the following paragraph:

Figure 47 is a scheme showing the method for constructing DNA fragment encoding the reconstructed 12B5 single chain Fv containing the linker sequence consisting of 15 amino acids **(SEQ ID NO: 89)** and the structure thereof.